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| <input type="checkbox"/> | L5 | L4 and avea | 1 |
| <input type="checkbox"/> | L4 | L3 and polyketide synthase | 51 |
| <input type="checkbox"/> | L3 | avermectin same avermitilis same (gene or nucleic acid or dna) | 80 |
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☐ 1. Document ID: US 6777543 B2

Using default format because multiple data bases are involved.

L4: Entry 1 of 51

File: USPT

Aug 17, 2004

US-PAT-NO: 6777543

DOCUMENT-IDENTIFIER: US 6777543 B2

TITLE: 13-methyl erythromycin derivatives

DATE-ISSUED: August 17, 2004

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|------------------|-----------|-------|----------|---------|
| Wu; Yong-Jin | Madison | CT | | |
| Su; Wei-Guo | East Lyme | CT | | |
| Kaneko; Takushi | Guilford | CT | | |
| McArthur; Hamish | Mystic | CT | | |

US-CL-CURRENT: 536/7.4; 536/7.2, 536/7.3

| | | | | | | | | | | | | |
|----------------------|-----------------------|--------------------------|-----------------------|------------------------|--------------------------------|----------------------|---------------------------|---------------------------|-----------------------------|------------------------|----------------------|--------------------------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KIMC | Drawings |
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☐ 2. Document ID: US 6759536 B2

L4: Entry 2 of 51

File: USPT

Jul 6, 2004

US-PAT-NO: 6759536

DOCUMENT-IDENTIFIER: US 6759536 B2

TITLE: Polynucleotides encoding the fkbA gene of the FK-520 polyketide synthase gene cluster

DATE-ISSUED: July 6, 2004

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---------------------|---------------|-------|----------|---------|
| Reeves; Christopher | Orinda | CA | | |
| Chu; Daniel | Santa Clara | CA | | |
| Khosla; Chaitan | Palo Alto | CA | | |
| Santi; Daniel | San Francisco | CA | | |
| Wu; Kai | Foster City | CA | | |

US-CL-CURRENT: 546/71

ABSTRACT:

Host cells comprising recombinant vectors encoding the FK-520 polyketide synthase and FK-520 modification enzymes can be used to produce the FK-520 polyketide. Recombinant DNA constructs comprising one or more FK-520 polyketide synthase domains, modules, open reading frames, and variants thereof can be used to produce recombinant polyketide synthases and a variety of different polyketides with application as pharmaceutical and veterinary products.

10 Claims, 13 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 9

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | RMBC | Drawing |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|

☐ 3. Document ID: US 6750040 B1

L4: Entry 3 of 51

File: USPT

Jun 15, 2004

US-PAT-NO: 6750040

DOCUMENT-IDENTIFIER: US 6750040 B1

TITLE: Cell-free synthesis of polyketides

DATE-ISSUED: June 15, 2004

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------|------------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Pieper; Rembert | Washington | DC | | |
| Luo; Guanglin | Providence | RI | | |
| Cane; David E. | Providence | RI | | |

US-CL-CURRENT: 435/41; 435/64

ABSTRACT:

Cell-free systems which effect the production of polyketides employing modular polyketide synthases are described. Libraries of new and/or known polyketides may also be produced in cell-free systems employing aromatic PKS, modular PKS or both.

15 Claims, 8 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

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|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | RMBC | Drawing |
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☐ 4. Document ID: US 6689611 B1

L4: Entry 4 of 51

File: USPT

Feb 10, 2004

US-PAT-NO: 6689611

DOCUMENT-IDENTIFIER: US 6689611 B1

TITLE: Modified Streptomyces host cells for increased avermectin production and methods of making the same

DATE-ISSUED: February 10, 2004

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|--------------------------|-----------|-------|----------|---------|
| Stutzman-Engwall; Kim J. | East Lyme | CT | | |
| Price; Brenda S. | Antioch | IL | | |

US-CL-CURRENT: 435/471; 435/76

ABSTRACT:

The present invention is directed to compositions and methods for producing avermectins, and is primarily in the field of animal health. The present invention relates to the identification and characterization of two novel genes, herein referred to as the aver1 and aver2 genes, that are involved in regulating avermectin polyketide synthase (PKS) expression and avermectin biosynthesis in Streptomyces avermitilis. The present invention is based on the discovery that inactivation of these genes results in an increase in the amount of avermectin produced by S. avermitilis.

4 Claims, 7 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 5

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-----|----------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | EMD | Drawings |
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☐ 5. Document ID: US 6670168 B1

L4: Entry 5 of 51

File: USPT

Dec 30, 2003

US-PAT-NO: 6670168

DOCUMENT-IDENTIFIER: US 6670168 B1

TITLE: Recombinant Streptomyces hygroscopicus host cells that produce 17-desmethyrapamycin

DATE-ISSUED: December 30, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|------------------|---------------|-------|----------|---------|
| Katz; Leonard | Oakland | CA | | |
| Liu; Lu | Redwood City | CA | | |
| Chung; Loleta M. | San Francisco | CA | | |

US-CL-CURRENT: 435/252.35

ABSTRACT:

Recombinant host cells that produce rapamycin analogues are constructed by deleting or modifying rapamycin biosynthetic gene cluster genes and are useful in the production of compounds used as antifungals, anticancers, immunosuppressants, and neurotrophins.

1 Claims, 2 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 2

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|----------|---------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Footnote | Drawing |
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☐ 6. Document ID: US 6660862 B2

L4: Entry 6 of 51

File: USPT

Dec 9, 2003

US-PAT-NO: 6660862

DOCUMENT-IDENTIFIER: US 6660862 B2

TITLE: Polyketide synthase enzymes and recombinant DNA constructs therefor

DATE-ISSUED: December 9, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---------------------|---------------|-------|----------|---------|
| Reeves; Christopher | Orinda | CA | | |
| Chu; Daniel | Santa Clara | CA | | |
| Khosla; Chaitan | Palo Alto | CA | | |
| Santi; Daniel | San Francisco | CA | | |
| Wu; Kai | Foster City | CA | | |

US-CL-CURRENT: 546/92

ABSTRACT:

Polyketide compounds of the formula but not including FK-506, FK-520, 18-hydroxy-FK520 and 18-hydroxy-FK-506. ##STR1##

46 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 9

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|----------|---------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Footnote | Drawing |
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☐ 7. Document ID: US 6632673 B1

L4: Entry 7 of 51

File: USPT

Oct 14, 2003

US-PAT-NO: 6632673

DOCUMENT-IDENTIFIER: US 6632673 B1

TITLE: Directing the ratio of B2:B1 avermectins in Streptomyces avermitilis host cells

DATE-ISSUED: October 14, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|--------------------------|---------------|-------|----------|---------|
| Stutzman-Engwall; Kim J. | East Lyme | CT | | |
| Chen; Yan | Santa Clara | CA | | |
| Gustafsson; Claes | Belmont | CA | | |
| Krebber; Anke | Mountain View | CA | | |
| Minshull; Jeremy | Menlo Park | CA | | |
| Raillard; Sun Ai | Mountain View | CA | | |

US-CL-CURRENT: 435/471; 435/252.35

ABSTRACT:

The present invention relates to polynucleotide molecules comprising nucleotide sequences encoding an aveC gene product, which polynucleotide molecules can be used to alter the ratio or amount of class 2:1 avermectins produced in fermentation cultures of S. avermitilis. The present invention further relates to vectors, host cells, and mutant strains of S. avermitilis in which the aveC gene has been inactivated, or mutated so as to change the ratio or amount of class 2:1 avermectins produced.

42 Claims, 10 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 7

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FIGS | Drawing |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|

☐ 8. Document ID: US 6627427 B1

L4: Entry 8 of 51

File: USPT

Sep 30, 2003

US-PAT-NO: 6627427

DOCUMENT-IDENTIFIER: US 6627427 B1

TITLE: Heterologous production of 15-methyl-6-deoxyerthronolide B

DATE-ISSUED: September 30, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---------------|---------|-------|----------|---------|
| Katz; Leonard | Oakland | CA | | |
| Revill; Peter | Oakland | CA | | |

US-CL-CURRENT: 435/252.3

ABSTRACT:

Recombinant host cells that comprise recombinant DNA expression vectors that drive expression of a product and a precursor for biosynthesis of that product can be used to produce useful products such as polyketides in host cells that do not naturally produce the product or produce the product at low levels due to the absence of the precursor or the presence of the precursor in rate limiting amounts.

12 Claims, 20 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 20

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|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|----------|--------------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Keywords | Drawing Data |
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☐ 9. Document ID: US 6583290 B1

L4: Entry 9 of 51

File: USPT

Jun 24, 2003

US-PAT-NO: 6583290

DOCUMENT-IDENTIFIER: US 6583290 B1

TITLE: 14-methyl epothilone derivatives

DATE-ISSUED: June 24, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|------------------|-------------|-------|----------|---------|
| Julien; Bryan | Oakland | CA | | |
| Katz; Leonard | Hayward | CA | | |
| Khosla; Chaitan | Palo Alto | CA | | |
| Tang; Li | Foster City | CA | | |
| Ziermann; Rainer | San Mateo | CA | | |

US-CL-CURRENT: 548/203; 181/205, 546/268.1

ABSTRACT:

Compounds of the invention include 14-methyl epothilone derivatives. More generally, preferred compounds of the invention are those that can be produced by altering the epothilone PKS genes as described herein and optionally by action of epothilone modification enzymes and/or by chemically modifying the resulting epothilones produced when those genes are expressed.

2 Claims, 9 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 8

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|----------|--------------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Keywords | Drawing Data |
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☐ 10. Document ID: US 6558942 B1

L4: Entry 10 of 51

File: USPT

May 6, 2003

US-PAT-NO: 6558942

DOCUMENT-IDENTIFIER: US 6558942 B1

TITLE: Combinatorial polyketide libraries produced using a modular PKS gene cluster as scaffold

DATE-ISSUED: May 6, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------|-----------|-------|----------|---------|
| Khosla; Chaitan | Palo Alto | CA | | |
| Kao; Camilla M. | Palo Alto | CA | | |

US-CL-CURRENT: 435/253.5; 435/4, 435/41, 435/76, 514/29, 536/7.1

ABSTRACT:

Combinatorial libraries of polyketides can be obtained by suitable manipulation of a host modular polyketide synthase gene cluster such as that which encodes the PKS for erythromycin. The combinatorial library is useful as a source of pharmaceutically active compounds. In addition, novel polyketides and antibiotics are prepared using this method.

53 Claims, 24 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 22

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| Full | Title | Citation | Front | Review | Classification | Data | Reference | Sequences | Attachments | Claims | Index | Drawings |
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☐ 11. Document ID: US 6531299 B1

L4: Entry 11 of 51

File: USPT

Mar 11, 2003

US-PAT-NO: 6531299

DOCUMENT-IDENTIFIER: US 6531299 B1

TITLE: Cell-free synthesis of polyketides

DATE-ISSUED: March 11, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------|------------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Pieper; Rembert | Washington | DC | | |
| Luo; Guanglin | Providence | RI | | |
| Cane; David E. | Providence | RI | | |

US-CL-CURRENT: [435/75](#); [435/76](#), [435/77](#), [435/78](#), [435/79](#), [435/80](#), [435/81](#), [435/82](#),
[435/83](#)

ABSTRACT:

Cell-free systems which effect the production of polyketides employing modular polyketide synthases are described. Libraries of new and/or known polyketides may also be produced in cell-free systems employing aromatic PKS, modular PKS or both.

15 Claims, 8 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

| | | | | | | | | | | | | |
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| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Full | Draw De |
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☐ 12. Document ID: US 6524841 B1

L4: Entry 12 of 51

File: USPT

Feb 25, 2003

US-PAT-NO: 6524841

DOCUMENT-IDENTIFIER: US 6524841 B1

TITLE: Recombinant megalomicin biosynthetic genes and uses thereof

DATE-ISSUED: February 25, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|----------------------|------------|-------|----------|---------|
| McDaniel; Robert | Palo Alto | CA | | |
| Volchegursky; Yanina | Emeryville | CA | | |

US-CL-CURRENT: [435/252.3](#); [435/252.35](#), [435/254.11](#), [435/320.1](#), [435/325](#), [435/419](#),
[536/23.1](#), [536/23.2](#), [536/23.7](#)

ABSTRACT:

Recombinant nucleic acids that encode all or a portion of the megAI gene of the megalomicin polyketide synthase (PKS) of *Micromonospora megalomicea* are used to produce recombinant PKS enzymes in host cells to make megalomicin, megalomicin derivatives, and other polyketides that are useful as antibiotics, motilides, and antiparasitics.

7 Claims, 70 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 70

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| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Full | Draw De |
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☐ 13. Document ID: US 6511841 B2

L4: Entry 13 of 51

File: USPT

Jan 28, 2003

US-PAT-NO: 6511841

DOCUMENT-IDENTIFIER: US 6511841 B2

TITLE: Streptomyces avermitilis gene directing the ratio of B2:B1 avermectins

DATE-ISSUED: January 28, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|--------------------------|-------------|-------|----------|---------|
| Stutzman-Engwall; Kim J. | East Lyme | CT | | |
| McArthur; Hamish | Gales Ferry | CT | | |
| Katoh; Yoshihiro | Aichi | | | JP |

US-CL-CURRENT: 435/253.5, 435/119, 435/252.3, 435/252.35, 435/320.1, 435/440,
435/471, 435/476, 435/486, 435/70.1, 435/75, 435/76, 530/350, 536/23.1, 536/23.7,
536/23.74, 536/7.1

ABSTRACT:

The present invention relates to polynucleotide molecules comprising nucleotide sequences encoding an aveC gene product, which polynucleotide molecules can be used to alter the ratio or amount of class 2:1 avermectins produced in fermentation cultures of S. avermitilis. The present invention further relates to vectors, host cells, and mutant strains of S. avermitilis in which the aveC gene has been inactivated, or mutated so as to change the ratio or amount of class 2:1 avermectins produced.

18 Claims, 10 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 7

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☐ 14. Document ID: US 6509455 B1

L4: Entry 14 of 51

File: USPT

Jan 21, 2003

US-PAT-NO: 6509455

DOCUMENT-IDENTIFIER: US 6509455 B1

TITLE: Recombinant narbonolide polyketide synthase

DATE-ISSUED: January 21, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---------------------|---------------|-------|----------|---------|
| Ashley; Gary | Alameda | CA | | |
| Betlach; Melanie C. | Burlingame | CA | | |
| Betlach; Mary | San Francisco | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |
| Tang; Li | Foster City | CA | | |

US-CL-CURRENT: 536/23.2; 435/193, 435/320.1, 536/23.7

ABSTRACT:

Recombinant DNA compounds that encode all or a portion of the narbonolide polyketide synthase are used to express recombinant polyketide synthase genes in host cells for the production of narbonolide, narbonolide derivatives, and polyketides that are useful as antibiotics and as intermediates in the synthesis of compounds with pharmaceutical value.

2 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

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|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FIGS | Drawing |
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☐ 15. Document ID: US 6509159 B2

L4: Entry 15 of 51

File: USPT

Jan 21, 2003

US-PAT-NO: 6509159

DOCUMENT-IDENTIFIER: US 6509159 B2

TITLE: Methods related to *Streptomyces avermitilis* gene directing the ratio of B2:B1 avermectins

DATE-ISSUED: January 21, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|--------------------------|-------------|-------|----------|---------|
| Stutzman-Engwall; Kim J. | East Lyme | CT | | |
| McArthur; Hamish | Gales Ferry | CT | | |
| Kato; Yoshihiro | Aichi | | | JP |

US-CL-CURRENT: 435/6; 435/76

ABSTRACT:

The present invention relates to polynucleotide molecules comprising nucleotide sequences encoding the aveC gene product, which polynucleotide molecules can be used to alter the ratio or amount of class 2:1 avermectins produced in fermentation cultures of *Streptomyces avermitilis*. The present invention further relates to vectors, host cells, and mutant strains of *Streptomyces avermitilis* in which the aveC gene has been inactivated, or mutated so as to change the ratio or amount of class 2:1 avermectins produced.

2 Claims, 10 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 7

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FIGS | Drawing |
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☐ 16. Document ID: US 6503741 B1

L4: Entry 16 of 51

File: USPT

Jan 7, 2003

US-PAT-NO: 6503741

DOCUMENT-IDENTIFIER: US 6503741 B1

TITLE: Polyketide synthase genes from *Streptomyces venezuelae*

DATE-ISSUED: January 7, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---------------------|---------------|-------|----------|---------|
| Ashley; Gary | Alameda | CA | | |
| Betlach; Melanie C. | Burlingame | CA | | |
| Betlach; Mary | San Francisco | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |
| Tang; Li | Foster City | CA | | |

US-CL-CURRENT: 435/183, 435/189, 435/193, 435/232, 435/252.33, 435/252.35,
435/254.2, 435/320.1, 536/23.1, 536/23.2, 536/23.7

ABSTRACT:

Combinatorial libraries of polyketides can be obtained by suitable manipulation of a host modular polyketide synthase gene cluster such as that which encodes the PKS for picromycin. The combinatorial library is useful as a source of pharmaceutically active compounds. In addition, novel polyketides and antibiotics are prepared using this method.

16 Claims, 37 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 30

| | | | | | | | | | | | | |
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| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FIGURE | Drawings |
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☐ 17. Document ID: US 6503737 B1

L4: Entry 17 of 51

File: USPT

Jan 7, 2003

US-PAT-NO: 6503737

DOCUMENT-IDENTIFIER: US 6503737 B1

TITLE: Isolated nucleic acids relating to the fkbA gene within the FK-520
polyketide synthase gene cluster

DATE-ISSUED: January 7, 2003

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---------------------|--------|-------|----------|---------|
| Reeves; Christopher | Orinda | CA | | |

| | | |
|-----------------|---------------|----|
| Chu; Daniel | Santa Clara | CA |
| Khosla; Chaitan | Palo Alto | CA |
| Santi; Daniel | San Francisco | CA |
| Wu; Kai | Foster City | CA |

US-CL-CURRENT: 435/76; 435/252.3, 435/252.35, 435/320.1, 536/23.1, 536/23.2

ABSTRACT:

Host cells comprising recombinant vectors encoding the FK-520 polyketide synthase and FK-520 modification enzymes can be used to produce the FK-520 polyketide. Recombinant DNA constructs comprising one or more FK-520 polyketide synthase domains, modules, open reading frames, and variants thereof can be used to produce recombinant polyketide synthases and a variety of different polyketides with application as pharmaceutical and veterinary products.

34 Claims, 8 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 9

| | | | | | | | | | | | | |
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| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Foot | Draw. B |
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☐ 18. Document ID: US 6500960 B1

L4: Entry 18 of 51

File: USPT

Dec 31, 2002

US-PAT-NO: 6500960

DOCUMENT-IDENTIFIER: US 6500960 B1

TITLE: Method to produce novel polyketides

DATE-ISSUED: December 31, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------|------------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Pieper; Rembert | Washington | DC | | |
| Luo; Guanglin | Madison | CT | | |
| Cane; David E. | Providence | RI | | |
| Kao; Camilla | Palo Alto | CA | | |

US-CL-CURRENT: 549/264

ABSTRACT:

Modified PKS gene clusters which produce novel polyketides in an efficient system in a host cell or in a cell free extract are described. The novel polyketides result from the incorporation of diketides of the formula ##STR1##

wherein A is a moiety that activates the diketide, and at least one of R.sup.1 and R.sup.2 is a substituent other than that natively occurring in the diketide normally processed by the modified PKS cluster. The polyketides may also be

glycosylated to provide antibiotics.

17 Claims, 5 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 5

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FullC | Drawing |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-------|---------|
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-------|---------|

☐ 19. Document ID: US 6495318 B2

L4: Entry 19 of 51

File: USPT

Dec 17, 2002

US-PAT-NO: 6495318

DOCUMENT-IDENTIFIER: US 6495318 B2

TITLE: Method and kits for preparing multicomponent nucleic acid constructs

DATE-ISSUED: December 17, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|------------------|---------------------|-------|----------|---------|
| Harney; Peter D. | late of Aliso Viejo | CA | | |

US-CL-CURRENT: 435/6; 435/254.2, 435/320.1, 435/91.1, 435/91.2, 536/22.1, 536/24.3, 536/24.33, 536/24.5

ABSTRACT:

The invention provides a highly efficient, rapid, and cost effective method of linking nucleic acid components in a predetermined order to produce a nucleic acid multicomponent construct. The invention further provides nucleic acid components, each nucleic acid component comprising a double stranded nucleic acid molecule having at least one single stranded 5' or 3' terminal sequence, the terminal sequence having sufficient complementarity to either a terminal sequence in a separate nucleic acid component or to a sequence in a linking nucleic acid molecule so as to allow for specific annealing of complementary sequences and linkage of the components in a predetermined order. Kits containing reagents required to practice the method of the invention are also provided.

43 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 5

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FullC | Drawing |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-------|---------|
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-------|---------|

☐ 20. Document ID: US 6472371 B1

L4: Entry 20 of 51

File: USPT

Oct 29, 2002

US-PAT-NO: 6472371

DOCUMENT-IDENTIFIER: US 6472371 B1

TITLE: Macrolides

DATE-ISSUED: October 29, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|----------------------------------|-------------|-------|----------|---------|
| Dirlam; John Philip | Gales Ferry | CT | | |
| McArthur; Hamish Alastair Irvine | Mystic | CT | | |
| Blize; Alan Elwood | New London | CT | | |

US-CL-CURRENT: 514/29; 536/124, 536/7.2, 536/7.4

ABSTRACT:

The invention relates to novel erythromycin analogs and azalides, particularly ones with novel C-13 substituents, and to pharmaceutically acceptable salts thereof. The compounds of this invention are antibacterial agents that may be used to treat various bacterial and protozoa infections. The invention also relates to pharmaceutical compositions containing such compounds and to methods of treating bacterial protozoa infections by administering such compounds. The invention also relates to methods of preparing such compounds and to intermediates useful in such preparation.

9 Claims, 0 Drawing figures

Exemplary Claim Number: 1

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|--------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | MMIC | Draw D |
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☐ 21. Document ID: US 6461838 B2

Using default format because multiple data bases are involved.

L4: Entry 21 of 51

File: USPT

Oct 8, 2002

US-PAT-NO: 6461838

DOCUMENT-IDENTIFIER: US 6461838 B2

TITLE: Recombinant production of novel polyketides

DATE-ISSUED: October 8, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------------|-----------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Hopwood; David A. | Norwich | | | GB |
| Ebert-Khosla; Suzanne | Stanford | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |
| Fu; Hong | Stanford | CA | | |
| Kao; Camilla | Stanford | CA | | |

US-CL-CURRENT: 435/91.1; 435/183, 435/252.31, 435/252.33, 435/320.1, 536/23.1, 536/23.2

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|--------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FWOC | Draw D |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|--------|

☐ 22. Document ID: US 6437151 B2

L4: Entry 22 of 51

File: USPT

Aug 20, 2002

US-PAT-NO: 6437151

DOCUMENT-IDENTIFIER: US 6437151 B2

TITLE: Erythromycins and process for their preparation

DATE-ISSUED: August 20, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|------------------------|-----------|-------|----------|---------|
| Leadlay; Peter Francis | Cambridge | | | GB |
| Staunton; James | Cambridge | | | GB |
| Cortes; Jesus | Cambridge | | | GB |

Pacey; Michael Stephen

Broadstairs

GB

US-CL-CURRENT: 549/271; 536/7.2, 549/13, 549/266, 549/29

ABSTRACT:

Erythromycins, particularly ones with novel C-13 substituents R1 (e.g. C.sub.3 - C.sub.6 cycloalkyl or cycloalkenyl groups) are prepared by fermenting suitable organisms in the presence of R.sub.1 CO.sub.2 H. A preferred organism is Saccharopolyspora erythraea preferably containing an integrated plasmid capable of directing synthesis of desired compounds.

10 Claims, 16 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 16

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Footnote | Drawing |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|----------|---------|
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☐ 23. Document ID: US 6410301 B1

L4: Entry 23 of 51

File: USPT

Jun 25, 2002

US-PAT-NO: 6410301

DOCUMENT-IDENTIFIER: US 6410301 B1

TITLE: Myxococcus host cells for the production of epothilones

DATE-ISSUED: June 25, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------|-----------|-------|----------|---------|
| Julien; Bryan | Oakland | CA | | |
| Katz; Leonard | Hayward | CA | | |
| Khosla; Chaitan | Palo Alto | CA | | |

US-CL-CURRENT: 435/252.3

ABSTRACT:

Recombinant Myxococcus host cell containing recombinant expression vectors containing epothilone polyketide synthase genes can produce epothilones C and D.

6 Claims, 4 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 4

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Footnote | Drawing |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|----------|---------|
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|----------|---------|

☐ 24. Document ID: US 6399382 B1

L4: Entry 24 of 51

File: USPT

Jun 4, 2002

US-PAT-NO: 6399382

DOCUMENT-IDENTIFIER: US 6399382 B1

**** See image for Certificate of Correction ****

TITLE: Recombinant production of novel polyketides

DATE-ISSUED: June 4, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------------|-----------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Hopwood; David A. | Norwich | | | GB |
| Ebert-Khosla; Susanne | Stanford | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |
| Kao; Camilla | Stanford | CA | | |

US-CL-CURRENT: 435/440; 435/183, 435/189, 435/232, 435/252.3, 435/252.35,
435/320.1, 435/471, 435/486

ABSTRACT:

Novel polyketides and novel methods of efficiently producing both new and known polyketides, using recombinant technology, are disclosed. In particular, a novel host-vector system is described which is used to produce polyketide synthases which in turn catalyze the production of a variety of polyketides.

15 Claims, 15 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 13

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Publ | Draw |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|

☐ 25. Document ID: US 6391594 B1

L4: Entry 25 of 51

File: USPT

May 21, 2002

US-PAT-NO: 6391594

DOCUMENT-IDENTIFIER: US 6391594 B1

TITLE: Modified modular PKS with retained scaffold

DATE-ISSUED: May 21, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------|----------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Ashley; Gary | Alameda | CA | | |
| Fu; Hong | Stanford | CA | | |
| Kao; Camilla M. | Stanford | CA | | |

McDaniel; Robert Palo Alto CA

US-CL-CURRENT: 435/91.4; 435/183, 435/193, 435/252.35, 435/320.1, 435/455, 435/471,
435/486, 536/23.2

ABSTRACT:

Combinatorial libraries of polyketides can be obtained by suitable manipulation of a host modular polyketide synthase gene cluster such as that which encodes the PKS for erythromycin. The combinatorial library is useful as a source of pharmaceutically active compounds.

16 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 8

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Publ | Draw |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|
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☐ 26. Document ID: US 6358712 B1

L4: Entry 26 of 51

File: USPT

Mar 19, 2002

US-PAT-NO: 6358712

DOCUMENT-IDENTIFIER: US 6358712 B1

TITLE: Ordered gene assembly

DATE-ISSUED: March 19, 2002

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|--------------------|-----------|-------|----------|---------|
| Jarrell; Kevin A. | Lincoln | MA | | |
| Coljee; Vincent W. | Cambridge | MA | | |
| Donahue; William | Quincy | MA | | |
| Mikheeva; Svetlana | Allston | MA | | |

US-CL-CURRENT: 435/91.1; 435/6, 435/91.2, 435/91.3, 435/91.52, 536/23.1

ABSTRACT:

The present invention provides an improved system for linking nucleic acids to one another. In particular, the present invention provides techniques for producing DNA product molecules that may be easily and directly ligated to recipient molecules. The product molecules need not be cleaved with restriction enzymes in order to undergo such ligation. In preferred embodiments of the invention, the DNA product molecules are produced through iterative DNA synthesis reactions, so that the product molecules are amplified products. The invention further provides methods for directed ligation of product molecules (i.e., for selective ligation of certain molecules within a collection of molecules), and also for methods of exon shuffling, in which multiple different product molecules are produced in a single ligation reaction. Preferred embodiments of the invention involve ligation of product molecules encoding functional protein domains, particularly domains naturally found in conserved gene families. The inventive DNA manipulation system

is readily integrated with other nucleic acid manipulation systems, such as ribozyme-mediated systems, and also is susceptible to automation.

29 Claims, 48 Drawing figures

Exemplary Claim Number: 1,2

Number of Drawing Sheets: 46

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FIGURE | Drawing |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|--------|---------|
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☐ 27. Document ID: US 6303767 B1

L4: Entry 27 of 51

File: USPT

Oct 16, 2001

US-PAT-NO: 6303767

DOCUMENT-IDENTIFIER: US 6303767 B1

TITLE: Nucleic acids encoding narbonolide polyketide synthase enzymes from streptomyces narbonensis

DATE-ISSUED: October 16, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---------------------|---------------|-------|----------|---------|
| Betlach; Melanie C. | San Francisco | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |

US-CL-CURRENT: 536/23.2; 435/320.1, 536/23.1

ABSTRACT:

Host cells comprising recombinant vectors encoding the narbomycin polyketide synthase and narbomycin modification enzymes from Streptomyces narbonensis can be used to produce narbomycin, picromycin, methymycin, and neomethymycin. Recombinant DNA constructs comprising one or more narbomycin polyketide synthase domains, modules, open reading frames, and variants thereof can be used to produce recombinant polyketide synthases and a variety of different polyketides with application in agriculture, medicine, and animal health.

9 Claims, 2 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 2

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FIGURE | Drawing |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|--------|---------|
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|--------|---------|

☐ 28. Document ID: US 6303342 B1

L4: Entry 28 of 51

File: USPT

Oct 16, 2001

US-PAT-NO: 6303342

DOCUMENT-IDENTIFIER: US 6303342 B1

TITLE: Recombinant methods and materials for producing epothilones C and D

DATE-ISSUED: October 16, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------|-------------|-------|----------|---------|
| Julien; Bryan | Oakland | CA | | |
| Katz; Leonard | Hayward | CA | | |
| Khosla; Chaitan | Palo Alto | CA | | |
| Tang; Li | Foster City | CA | | |

US-CL-CURRENT: 435/76

ABSTRACT:

Recombinant nucleic acids that encode all or a portion of the epothilone polyketide synthase (PKS) are used to express recombinant PKS genes in host cells for the production of epothilones, epothilone derivatives, and polyketides that are useful as cancer chemotherapeutics, fungicides, and immunosuppressants.

29 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 8

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-----|----------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | MMO | Draw. De |
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☐ 29. Document ID: US 6271255 B1

L4: Entry 29 of 51

File: USPT

Aug 7, 2001

US-PAT-NO: 6271255

DOCUMENT-IDENTIFIER: US 6271255 B1

TITLE: Erythromycins and process for their preparation

DATE-ISSUED: August 7, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|------------------------|-------------|-------|----------|---------|
| Leadlay; Peter Francis | Cambridge | | | GB |
| Staunton; James | Cambridge | | | GB |
| Cortes; Jesus | Cambridge | | | GB |
| Pacey; Michael Stephen | Broadstairs | | | GB |

US-CL-CURRENT: 514/450; 514/29, 536/7.2, 549/13, 549/266, 549/271, 549/29

ABSTRACT:

Erythromycins, particularly with C-13 substituents R1 (e.g. C.sub.3 -C.sub.6 cycloalkyl or cycloalkenyl groups) are prepared by fermenting suitable organisms in the presence of R.sub.1 CO.sub.2 H. A preferred organism is Saccharopolyspora

erythraea preferably containing an integrated plasmid capable of directing synthesis of desired compounds.

27 Claims, 16 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 16

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Exemplary | Drawing |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-----------|---------|
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-----------|---------|

☐ 30. Document ID: US 6262340 B1

L4: Entry 30 of 51

File: USPT

Jul 17, 2001

US-PAT-NO: 6262340

DOCUMENT-IDENTIFIER: US 6262340 B1

**** See image for Certificate of Correction ****

TITLE: Production of polyketides in plants

DATE-ISSUED: July 17, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|------------------|---------------|-------|----------|---------|
| Betlach; Mary C. | San Francisco | CA | | |
| Kealey; James T. | Davis | CA | | |
| Gutterson; Neal | Oakland | CA | | |
| Ralston; Ed | Pleasant Hill | CA | | |

US-CL-CURRENT: 800/278; 435/410, 435/411, 435/419, 435/69.1, 800/281, 800/284

ABSTRACT:

The present invention provides genetically altered plants and plant cells that have been modified to contain expression system(s) capable of expressing a functional polyketide synthase (PKS). The present invention further provides methods of producing PKS and polyketides using these plants and cells.

65 Claims, 3 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 3

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Exemplary | Drawing |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-----------|---------|
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☐ 31. Document ID: US 6261816 B1

L4: Entry 31 of 51

File: USPT

Jul 17, 2001

US-PAT-NO: 6261816

DOCUMENT-IDENTIFIER: US 6261816 B1

TITLE: Method to produce novel polyketides

DATE-ISSUED: July 17, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------|------------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Pieper; Rembert | Washington | DC | | |
| Luo; Guanglin | Madison | CT | | |
| Cane; David E. | Providence | RI | | |
| Kao; Camilla | Palo Alto | CA | | |

US-CL-CURRENT: [435/183](#); [435/91.1](#), [435/91.4](#), [435/91.41](#), [435/91.42](#), [536/23.2](#)

ABSTRACT:

Modified PKS gene clusters which produce novel polyketides in an efficient system in a host cell or in a cell free extract are described.

10 Claims, 3 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 3

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Publ | Draw |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|

☐ 32. Document ID: US 6251636 B1

L4: Entry 32 of 51

File: USPT

Jun 26, 2001

US-PAT-NO: 6251636

DOCUMENT-IDENTIFIER: US 6251636 B1

TITLE: Recombinant oleandolide polyketide synthase

DATE-ISSUED: June 26, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|--------------------------|---------------|-------|----------|---------|
| Betlach; Mary C. | San Francisco | CA | | |
| Shah; Sanjay Krishnakant | Concord | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |
| Tang; Li | Foster City | CA | | |

US-CL-CURRENT: [435/76](#); [435/252.35](#), [435/254.2](#), [435/320.1](#), [435/325](#), [435/419](#), [536/23.1](#), [536/23.2](#)

ABSTRACT:

Recombinant DNA compounds that encode all or a portion of the oleandolide polyketide synthase are used to express recombinant polyketide synthase genes in host cells for the production of oleandolide, oleandolide derivatives, and

polyketides that are useful as antibiotics and motilides.

22 Claims, 5 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Form | Draw. De |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|----------|
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☐ 33. Document ID: US 6248579 B1

L4: Entry 33 of 51

File: USPT

Jun 19, 2001

US-PAT-NO: 6248579

DOCUMENT-IDENTIFIER: US 6248579 B1

**** See image for Certificate of Correction ****

TITLE: Streptomyces avermitilis gene directing the ratio of B2:B1 avermectins

DATE-ISSUED: June 19, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|--------------------------|-------------|-------|----------|---------|
| Stutzman-Engwall; Kim J. | East Lyme | CT | | |
| McArthur; Hamish | Gales Ferry | CT | | |
| Kato; Yoshihiro | Aichi | | | JP |

US-CL-CURRENT: 435/253.5; 435/119, 435/471, 435/75, 435/76, 536/23.1, 536/7.1

ABSTRACT:

The present invention relates to polynucleotide molecules comprising nucleotide sequences encoding an aveC gene product, which polynucleotide molecules can be used to alter the ratio or amount of class 2:1 avermectins produced in fermentation cultures of S. avermitilis. The present invention further relates to vectors, host cells, and mutant strains of S. avermitilis in which the aveC gene has been inactivated, or mutated so as to change the ratio or amount of class 2:1 avermectins produced.

14 Claims, 10 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 7

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Form | Draw. De |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|----------|
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☐ 34. Document ID: US 6215007 B1

L4: Entry 34 of 51

File: USPT

Apr 10, 2001

US-PAT-NO: 6215007

DOCUMENT-IDENTIFIER: US 6215007 B1

**** See image for Certificate of Correction ****

TITLE: Recombinant production of novel polyketides

DATE-ISSUED: April 10, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------------|-----------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Hopwood; David A. | Norwich | | | GB |
| Ebert-Khosla; Suzanne | Stanford | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |
| Fu; Hong | Stanford | CA | | |

US-CL-CURRENT: 549/417; 549/389, 549/400, 560/128, 562/433, 562/435, 562/461

ABSTRACT:

Novel polyketides and novel methods of efficiently producing both new and known polyketides, using recombinant technology, are disclosed. In particular, a novel host-vector system is described which is used to produce polyketide synthases which in turn catalyze the production of a variety of polyketides.

20 Claims, 32 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 26

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|----------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FIGS | Draw. Ds |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|----------|

☐ 35. Document ID: US 6214573 B1

L4: Entry 35 of 51

File: USPT

Apr 10, 2001

US-PAT-NO: 6214573

DOCUMENT-IDENTIFIER: US 6214573 B1

TITLE: Recombinant production of novel polyketides

DATE-ISSUED: April 10, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------------|-----------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Hopwood; David A. | Norwich | | | GB |
| Ebert-Khosla; Suzanne | Stanford | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |
| Fu; Hong | Stanford | CA | | |

US-CL-CURRENT: 435/41; 435/132, 435/133, 435/147, 435/148, 435/252.3, 435/252.33, 435/252.35

ABSTRACT:

Novel polyketides and novel methods of efficiently producing both new and known polyketides, using recombinant technology, are disclosed. In particular, a novel host-vector system is described which is used to produce polyketide synthases which in turn catalyze the production of a variety of polyketides.

21 Claims, 15 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 13

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Full | Draw |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|

☐ 36. Document ID: US 6197591 B1

L4: Entry 36 of 51

File: USPT

Mar 6, 2001

US-PAT-NO: 6197591

DOCUMENT-IDENTIFIER: US 6197591 B1

TITLE: *Streptomyces avermitilis* regulatory genes for increased avermectin production

DATE-ISSUED: March 6, 2001

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|--------------------------|-----------|-------|----------|---------|
| Stutzman-Engwall; Kim J. | East Lyme | CT | | |
| Price; Brenda S. | Antioch | IL | | |

US-CL-CURRENT: 435/486; 435/183, 435/252.3, 435/253.5, 435/254.11, 435/320.1, 435/325, 435/419, 435/69.1, 435/76

ABSTRACT:

The present invention is directed to compositions and methods for producing avermectins, and is primarily in the field of animal health. The present invention relates to the identification and characterization of two novel genes, herein referred to as the aveR1 and aveR2 genes, that are involved in regulating avermectin polyketide synthase (PKS) expression and avermectin biosynthesis in Streptomyces avermitilis. The present invention is based on the discovery that inactivation of these genes results in an increase in the amount of avermectin produced by S. avermitilis.

36 Claims, 4 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 5

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Full | Draw |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|

☐ 37. Document ID: US 6117659 A

L4: Entry 37 of 51

File: USPT

Sep 12, 2000

US-PAT-NO: 6117659

DOCUMENT-IDENTIFIER: US 6117659 A

TITLE: Recombinant narbonolide polyketide synthase

DATE-ISSUED: September 12, 2000

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---------------------|---------------|-------|----------|---------|
| Ashley; Gary | Alameda | CA | | |
| Betlach; Melanie C. | Burlingame | CA | | |
| Betlach; Mary | San Francisco | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |
| Tang; Li | Foster City | CA | | |

US-CL-CURRENT: 435/155; 435/132, 435/189, 435/252.3, 435/252.33, 435/252.35,
435/320.1, 536/23.2, 536/23.7

ABSTRACT:

Recombinant DNA compounds that encode all or a portion of the narbonolide polyketide synthase are used to express recombinant polyketide synthase genes in host cells for the production of narbonolide, narbonolide derivatives, and polyketides that are useful as antibiotics and as intermediates in the synthesis of compounds with pharmaceutical value.

11 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 7

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|--------|--------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FullID | Draw D |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|--------|--------|

☐ 38. Document ID: US 6077696 A

L4: Entry 38 of 51

File: USPT

Jun 20, 2000

US-PAT-NO: 6077696

DOCUMENT-IDENTIFIER: US 6077696 A

TITLE: Recombinant production of novel polyketides

DATE-ISSUED: June 20, 2000

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-------------------|----------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Hopwood; David A. | Norwich | | | GB |

| | | |
|-----------------------|-----------|----|
| Ebert-Khosla; Suzanne | Stanford | CA |
| McDaniel; Robert | Palo Alto | CA |
| Fu; Hong | Stanford | CA |
| Kao; Camilla | Stanford | CA |

US-CL-CURRENT: 435/135; 435/132, 435/147, 435/148, 435/183, 435/252.3, 435/252.33, 435/252.35, 435/320.1, 536/23.1, 536/23.2

ABSTRACT:

Novel polyketides and novel methods of efficiently producing both new and known polyketides, using recombinant technology, are disclosed. In particular, a novel host-vector system is described which is used to produce polyketide synthases which in turn catalyze the production of a variety of polyketides.

6 Claims, 33 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 26

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-------|----------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | PublC | Drawn On |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-------|----------|

☐ 39. Document ID: US 6066721 A

L4: Entry 39 of 51

File: USPT

May 23, 2000

US-PAT-NO: 6066721

DOCUMENT-IDENTIFIER: US 6066721 A

**** See image for Certificate of Correction ****

TITLE: Method to produce novel polyketides

DATE-ISSUED: May 23, 2000

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------|------------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CT | | |
| Pieper; Rembert | Menlo Park | CA | | |
| Luo; Guanglin | Providence | RI | | |
| Cane; David E. | Providence | RI | | |
| Kao; Camilla | Palo Alto | CA | | |

US-CL-CURRENT: 536/23.1; 435/252.3, 435/252.35, 435/320.1, 435/7.1, 536/23.2

ABSTRACT:

Modified PKS gene clusters which produce novel polyketides in an efficient system in a host cell or in a cell free extract are described.

12 Claims, 3 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 3

40. Document ID: US 6022731 A

Feb 8, 2000

DOCUMENT-IDENTIFIER: US 6022731 A

TITLE: Recombinant production of novel polyketides

DATE-ISSUED: February 8, 2000

INVENTOR - INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------------|-----------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Hopwood; David A. | Norwich | | | GB |
| Ebert-Khosla; Suzanne | Stanford | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |

US-CL-CURRENT: 435/252.35, 435/252.3, 435/252.33, 435/320.1, 435/471, 435/476,
536/23.1, 536/23.2, 536/23.7

ABSTRACT:

Novel polyketides and novel methods of efficiently producing both new and known polyketides, using recombinant technology, are disclosed. In particular, a novel host-vector system is described which is used to produce polyketide synthases which in turn catalyze the production of a variety of polyketides.

45 Claims, 14 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 13

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[Generate CACS](#)

| Terms | Documents |
|----------------------------|-----------|
| L3 and polyketide synthase | 51 |

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Fwd Refs

Bkwd Refs

Generate OACS

Search Results - Record(s) 41 through 51 of 51 returned.☐ 41. Document ID: US 5976830 A**Using default format because multiple data bases are involved.**

L4: Entry 41 of 51

File: USPT

Nov 2, 1999

US-PAT-NO: 5976830

DOCUMENT-IDENTIFIER: US 5976830 A

**** See image for Certificate of Correction ****

TITLE: Methods of producing doxorubicin

DATE-ISSUED: November 2, 1999

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---------------------|----------|-------|----------|---------|
| Strohl; William R. | Dublin | OH | | |
| Dickens; Michael L. | Columbus | OH | | |
| Desanti; Charles L. | Columbus | OH | | |

US-CL-CURRENT: 435/41; 435/189, 435/252.3, 435/252.33, 435/252.35, 435/320.1,
435/78, 536/23.1, 536/23.2, 536/23.7

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|-----------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Draw | Draw Data |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|-----------|

☐ 42. Document ID: US 5962293 A

L4: Entry 42 of 51

File: USPT

Oct 5, 1999

US-PAT-NO: 5962293

DOCUMENT-IDENTIFIER: US 5962293 A

TITLE: Methods of producing doxorubicin

DATE-ISSUED: October 5, 1999

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|---------------------|----------|-------|----------|---------|
| Strohl; William R. | Dublin | OH | | |
| Dickens; Michael L. | Columbus | OH | | |
| Desanti; Charles L. | Columbus | OH | | |

US-CL-CURRENT: 435/189; 435/183, 435/252.3, 435/252.33, 435/320.1, 536/23.2

ABSTRACT:

The present invention provides novel methods for producing doxorubicin using daunomycin as a substrate. One method employs a genetically engineered host microorganism which is transformed with a vector, preferably a plasmid, which contains the doxA gene. Preferably, the doxA gene, also referred to herein as "doxA", is cloned into a plasmid which is then introduced into the host microorganism, preferably a bacterial host, more preferably Streptomyces, to provide a transformed host microorganism. The doxA gene, when present on a plasmid, confers on the transformed host the ability to convert daunomycin and 13-dihydrodaunomycin, to doxorubicin. The doxA gene encodes a P450-like enzyme which catalyzes the hydroxylation of daunomycin and 13-dihydrodaunomycin at C-14 to form doxorubicin; such enzyme is designated "daunomycin C-14 hydroxylase". Thus, the expression of doxA in the transformed host using a plasmid which contains doxA enables the transformed host to convert daunomycin to doxorubicin. The doxorubicin is then extracted from host microorganism cultures.

4 Claims, 12 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 21

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | HTML | Draw D |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|--------|
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|--------|

☐ 43. Document ID: US 5962290 A

L4: Entry 43 of 51

File: USPT

Oct 5, 1999

US-PAT-NO: 5962290

DOCUMENT-IDENTIFIER: US 5962290 A

TITLE: Recombinant production of novel polyketides

DATE-ISSUED: October 5, 1999

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------------|-----------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Hopwood; David A. | Norwich | | | GB |
| Ebert-Khosla; Suzanne | Stanford | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |
| Fu; Hong | Stanford | CA | | |
| Kao; Camilla | Stanford | CA | | |

US-CL-CURRENT: 435/183; 435/252.3, 435/252.33, 435/252.35, 435/320.1, 435/471, 435/476, 536/23.1, 536/23.2, 536/23.7

ABSTRACT:

Novel polyketides and novel methods of efficiently producing both new and known polyketides, using recombinant technology, are disclosed. In particular, a novel host-vector system is described which is used to produce polyketide synthases which in turn catalyze the production of a variety of polyketides.

21 Claims, 33 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 26

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Draw | Draw |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|

☐ 44. Document ID: US 5945320 A

L4: Entry 44 of 51

File: USPT

Aug 31, 1999

US-PAT-NO: 5945320
DOCUMENT-IDENTIFIER: US 5945320 A

TITLE: Platenolide synthase gene

DATE-ISSUED: August 31, 1999

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------------|--------------|-------|----------|---------|
| Burgett; Stanley G. | Indianapolis | IN | | |
| Kuhstoss; Stuart A. | Indianapolis | IN | | |
| Rao; Ramachandra N. | Indianapolis | IN | | |
| Richardson; Mark A. | Bloomington | IN | | |
| Rosteck, Jr.; Paul R. | Indianapolis | IN | | |

US-CL-CURRENT: 435/183; 435/252.3, 435/252.35, 435/320.1, 435/69.1, 530/350,
536/23.2

ABSTRACT:

A DNA molecule isolated from Streptomyces ambofaciens encodes the multi-functional proteins which direct the synthesis of the polyketide platenolide.

25 Claims, 3 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 3

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | Draw | Draw |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|------|

☐ 45. Document ID: US 5876991 A

L4: Entry 45 of 51

File: USPT

Mar 2, 1999

US-PAT-NO: 5876991
DOCUMENT-IDENTIFIER: US 5876991 A

TITLE: Polyketide synthase genes

DATE-ISSUED: March 2, 1999

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------------|---------------|-------|----------|---------|
| DeHoff; Bradley S. | Indianapolis | IN | | |
| Kuhstoss; Stuart A. | Indianapolis | IN | | |
| Rosteck, Jr.; Paul R. | Indianapolis | IN | | |
| Sutton; Kimberly L. | New Palestine | IN | | |

US-CL-CURRENT: 435/183; 435/252.35, 435/320.1, 435/471, 435/486, 435/69.7,
536/23.2, 536/23.4

ABSTRACT:

A DNA molecule isolated from *Streptomyces fradiae* encodes the multi-functional proteins which direct the synthesis of the polyketide tylactone.

23 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-------|------------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | PubID | Grant Date |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|-------|------------|

☐ 46. Document ID: US 5843718 A

L4: Entry 46 of 51

File: USPT

Dec 1, 1998

US-PAT-NO: 5843718

DOCUMENT-IDENTIFIER: US 5843718 A

**** See image for Certificate of Correction ****

TITLE: Recombinant production of novel polyketides

DATE-ISSUED: December 1, 1998

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------------|-----------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Hopwood; David A. | Norwich | | | GB2 |
| Ebert-Khosla; Susanne | Stanford | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |
| Fu; Hong | Stanford | CA | | |

US-CL-CURRENT: 435/69.1; 435/183, 435/252.3, 435/325

ABSTRACT:

Novel polyketides and novel methods of efficiently producing both new and known polyketides, using recombinant technology, are disclosed. In particular, a novel host-vector system is described which is used to produce polyketide synthases which in turn catalyze the production of a variety of polyketides.

21 Claims, 15 Drawing figures

Exemplary Claim Number: 1
Number of Drawing Sheets: 13

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FIGS | Drawing |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|

☐ 47. Document ID: US 5830750 A

L4: Entry 47 of 51

File: USPT

Nov 3, 1998

US-PAT-NO: 5830750

DOCUMENT-IDENTIFIER: US 5830750 A

**** See image for Certificate of Correction ****

TITLE: Recombinant production of novel polyketides

DATE-ISSUED: November 3, 1998

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------------|----------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Hopwood; David A. | Norwich | | | GB2 |
| Ebert-Khosla; Suzanne | Stanford | CA | | |

US-CL-CURRENT: 435/252.35; 435/252.3, 435/254.11, 435/325

ABSTRACT:

Novel polyketides and novel methods of efficiently producing both new and known polyketides, using recombinant technology, are disclosed. In particular, a novel host-vector system is described which is used to produce polyketide synthases which in turn catalyze the production of a variety of polyketides.

8 Claims, 15 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 13

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FIGS | Drawing |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|

☐ 48. Document ID: US 5712146 A

L4: Entry 48 of 51

File: USPT

Jan 27, 1998

US-PAT-NO: 5712146

DOCUMENT-IDENTIFIER: US 5712146 A

**** See image for Certificate of Correction ****

TITLE: Recombinant combinatorial genetic library for the production of novel polyketides

DATE-ISSUED: January 27, 1998

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------------|-----------|-------|----------|---------|
| Khosla; Chaitan | Stanford | CA | | |
| Hopwood; David A. | Norwich | | | GB2 |
| Ebert-Khosla; Suzanne | Stanford | CA | | |
| McDaniel; Robert | Palo Alto | CA | | |
| Fu; Hong | Stanford | CA | | |
| Kao; Camilla | Stanford | CA | | |

US-CL-CURRENT: 435/252.35; 435/148, 435/156, 435/252.3, 435/252.33, 435/320.1,
536/23.1, 536/23.2, 536/23.7

ABSTRACT:

Novel polyketides and novel methods of efficiently producing both new and known polyketides, using recombinant technology, are disclosed. In particular, a novel host-vector system is described which is used to produce polyketide synthases which in turn catalyze the production of a variety of polyketides.

5 Claims, 33 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 26

| | | | | | | | | | | | | |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|
| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FIGS | Draw Ds |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|---------|

☐ 49. Document ID: US 5252474 A

L4: Entry 49 of 51

File: USPT

Oct 12, 1993

US-PAT-NO: 5252474

DOCUMENT-IDENTIFIER: US 5252474 A

TITLE: Cloning genes from Streptomyces avermitilis for avermectin biosynthesis and the methods for their use

DATE-ISSUED: October 12, 1993

INVENTOR-INFORMATION:

| NAME | CITY | STATE | ZIP CODE | COUNTRY |
|-----------------------|-----------|-------|----------|---------|
| Gewain; Keith M. | Middelsex | NJ | | |
| MacNeil; Douglas J. | Westfield | NJ | | |
| MacNeil; Tanya | Westfield | NJ | | |
| Paress; Philip S. | Maplewood | NJ | | |
| Ruby; Carolyn L. | Montclair | NJ | | |
| Streicher; Stanley L. | Verona | NJ | | |

US-CL-CURRENT: 435/91.1; 435/119, 435/252.33, 435/252.35, 435/320.1, 435/486,
435/488, 435/489, 435/76

ABSTRACT:

There are disclosed plasmids containing DNA isolated from Streptomyces avermitilis, the microorganism which is used to prepare avermectin compounds, identified as pAT1, pVE650 pVE855, pVE859, pVE1446, pVE923, and pVE924 which contain the genetic information for the biosynthesis of the avermectins. Methods for the isolation of such plasmid and for the manipulation of the plasmids to alter the formation of the avermectin compound are also disclosed.

46 Claims, 7 Drawing figures
Exemplary Claim Number: 24
Number of Drawing Sheets: 7

| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FIGS | Drawings |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|----------|
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|----------|

☐ 50. Document ID: EP 997528 A1

L4: Entry 50 of 51

File: EPAB

May 3, 2000

PUB-NO: EP000997528A1

DOCUMENT-IDENTIFIER: EP 997528 A1

TITLE: Streptomyces avermitilis regulatory genes for increased avermectin production

PUBN-DATE: May 3, 2000

INVENTOR-INFORMATION:

NAME

STUTZMAN-ENGWALL, KIM JONELLE

PRICE, BRENDA SUE

COUNTRY

US

US

INT-CL (IPC): C12 N 15/31; C12 N 15/76

EUR-CL (EPC): C07K014/36; C12N015/01, C12N015/76 , C12P019/62

ABSTRACT:

CHG DATE=20001128 STATUS=O> The present invention is directed to compositions and methods for producing avermectins, and is primarily in the field of animal health. The present invention relates to the identification and characterization of two novel genes, herein referred to as the aveR1 and aveR2 genes, that are involved in regulating avermectin polyketide synthase (PKS) expression and avermectin biosynthesis in Streptomyces avermitilis. The present invention is based on the discovery that inactivation of these genes results in an increase in the amount of

avermectin produced by S. avermitilis.



| Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | FIGS | Drawings |
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|----------|
|------|-------|----------|-------|--------|----------------|------|-----------|-----------|-------------|--------|------|----------|

☐ 51. Document ID: RU 2221042 C2, AU 9947575 A, JP 2000102394 A, EP 997528 A1, CA 2281935 A1, CN 1252440 A, CZ 9903232 A3, HU 9903073 A2, BR 9904109 A, KR 2000023111 A, US 6197591 B1, MX 9908462 A1, ZA 9905872 A, KR 343357 B, AU 758329 B,

US 6689611 B1

L4: Entry 51 of 51

File: DWPI

Jan 10, 2004

DERWENT-ACC-NO: 2000-318250

DERWENT-WEEK: 200414

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TITLE: Novel streptomyces avermitilis regulatory genes which when mutated are useful for increased production of avermectin useful as highly active parasitic agent for treating humans against parasite infections

INVENTOR: PRICE, B S; STUTZMAN-ENGWALL, K J

PRIORITY-DATA: 1998US-100134P (September 14, 1998), 1999US-0390721 (September 7, 1999), 2000US-0713893 (November 16, 2000)

PATENT-FAMILY:

| PUB-NO | PUB-DATE | LANGUAGE | PAGES | MAIN-IPC |
|------------------------|-------------------|----------|-------|------------|
| <u>RU 2221042 C2</u> | January 10, 2004 | | 000 | C12N015/31 |
| <u>AU 9947575 A</u> | March 23, 2000 | | 065 | C12N015/31 |
| <u>JP 2000102394 A</u> | April 11, 2000 | | 040 | C12N015/09 |
| <u>EP 997528 A1</u> | May 3, 2000 | E | 000 | C12N015/31 |
| <u>CA 2281935 A1</u> | March 14, 2000 | E | 000 | C12N015/11 |
| <u>CN 1252440 A</u> | May 10, 2000 | | 000 | C12N001/21 |
| <u>CZ 9903232 A3</u> | July 12, 2000 | | 000 | C12N001/20 |
| <u>HU 9903073 A2</u> | July 28, 2000 | | 000 | C12N015/31 |
| <u>BR 9904109 A</u> | October 17, 2000 | | 000 | C12P019/62 |
| <u>KR 2000023111 A</u> | April 25, 2000 | | 000 | C12N015/31 |
| <u>US 6197591 B1</u> | March 6, 2001 | | 000 | C12N015/76 |
| <u>MX 9908462 A1</u> | March 1, 2000 | | 000 | C12N015/57 |
| <u>ZA 9905872 A</u> | May 31, 2001 | | 070 | C12N000/00 |
| <u>KR 343357 B</u> | July 15, 2002 | | 000 | C12N015/31 |
| <u>AU 758329 B</u> | March 20, 2003 | | 000 | C12N015/31 |
| <u>US 6689611 B1</u> | February 10, 2004 | | 000 | C12N015/74 |

B1 INT-CL (IPC): A01 K 0/00; A01 N 63/02; A61 K 31/70; A61 K 31/7056; A61 K 48/00; C07 H 21/00; C07 K 14/195; C07 K 14/36; C07 K 16/12; C12 N 0/00; C12 N 1/15; C12 N 1/19; C12 N 1/20; C12 N 1/21; C12 N 5/10; C12 N 15/01; C12 N 15/09; C12 N 15/11; C12 N 15/31; C12 N 15/57; C12 N 15/63; C12 N 15/74; C12 N 15/76; C12 P 1/06; C12 P 17/08; C12 P 19/34; C12 P 19/62; C12 P 21/02; C12 P 21/08; C12 Q 1/68; C12 R 1/465; G01 N 33/15; G01 N 33/50; G01 N 33/569; G01 N 33/577; C12 P 19/62; C12 R 1:465; C12 N 15/31; C12 R 1:465; C12 N 1/21; C12 N 15/09; C12 P 21/02; C12 R 1:465; C12 R 1:465; C12 R 1:465; C12 P 1/06; C12 R 1:465

ABSTRACTED-PUB-NO: AU 9947575A

BASIC-ABSTRACT:

NOVELTY - Isolated polynucleotide molecule (I) encoding aver1 gene and aver2 gene products from Streptomyces avermitilis, is new.

DETAILED DESCRIPTION - Isolated polynucleotide molecule (I) encoding aver1 gene and aver2 gene products from Streptomyces avermitilis has a defined nucleotide sequence of 5045 base pairs given in the specification. The aver1 gene product has a protein

sequence of 401 amino acids (aa) and is encoded by an open reading frame (ORF) of nucleotides 1112 to 2317 of (I). The *aveR2* gene product has a protein sequence of 235 aa and is encoded by an ORF of nucleotides 2314 to 3021 of (I).

INDEPENDENT CLAIMS are also included for the following:

- (1) an isolated polynucleotide molecule (Ia) homologous to a polynucleotide molecule comprising nucleotides 1112 to 2317 of (I);
- (2) an isolated polynucleotide sequence (Ib) that naturally flanks the *aveR1* open reading frame (ORF) of *S. avermitilis* in situ comprising nucleotides 1-1111 and 2318-5045 of (I);
- (3) an isolated polynucleotide molecule (Ic) homologous to a polynucleotide molecule comprising nucleotides 2314 to 3021 of (I);
- (4) an isolated polynucleotide sequence (Id) that naturally flanks the *aveR2* open reading frame (ORF) of *S. avermitilis* in situ comprising nucleotides 1-2313 and 3022-5045 of (I);
- (5) an oligonucleotide molecule that hybridizes under highly stringent conditions to a polynucleotide comprising (I) or the complement of (I);
- (6) a recombinant vector (II) comprising (I);
- (7) a transformed host cell (III) comprising (II);
- (8) a substantially purified or isolated polypeptide (IV) comprising a sequence of 401 or 235 amino acids (as given in the specification), its homologous polypeptides or their fragments;
- (9) preparation (P1) of (IV);
- (10) a polynucleotide molecule (Ie) comprising (I) with at least one mutation that results in a detectable increase in the amount of avermectins produced by the cells of a strain of *S. avermitilis* compared to the cells of same strain that do not carry the gene mutation;
- (11) a genetic construct (GC) comprising (Ie) for introducing a mutation into either or both of the *aveR* genes;
- (12) identifying a mutation in the *aveR* genes in a species or strain of *S. avermitilis* by comparing the amounts of avermectin produced by mutant and non-mutant strains and detecting the mutation from the increased amount of avermectins produced by the mutant strains;
- (13) preparation (P2) of genetically modified cells of *S. avermitilis*;
- (14) a strain of *Streptomyces*, producing increased amount of avermectins as a result of mutation in *aveR* genes; and
- (15) an antibody (Ab) directed against *aveR1* or *aveR2* gene product.

ACTIVITY - Antiparasitic; insecticide.

MECHANISM OF ACTION - Avermectin polyketide synthase regulator. No supporting data given.

USE - (I) is useful for increased production of avermectins which comprises culturing the cells of species or strains of *Streptomyces* comprising mutated *aveR*

genes (claimed). (Ie) is useful to mutate aveR genes (claimed). Avermectins are highly active anti parasitic agents having particular utility as anthelmintics, ectoparasiticides, insecticides and acaricides and useful for treating various diseases or conditions in humans, particularly those caused by parasitic infections.

ADVANTAGE - Avermectins prepared are effective against various nematodes, parasites including gastrointestinal parasites, ectoparasites, insects and other organisms, thus providing a wide range of treatment.

ABSTRACTED-PUB-NO:

US 6197591B EQUIVALENT-ABSTRACTS:

NOVELTY - Isolated polynucleotide molecule (I) encoding aveR1 gene and aveR2 gene products from *Streptomyces avermitilis*, is new.

DETAILED DESCRIPTION - Isolated polynucleotide molecule (I) encoding aveR1 gene and aveR2 gene products from *Streptomyces avermitilis* has a defined nucleotide sequence of 5045 base pairs given in the specification. The aveR1 gene product has a protein sequence of 401 amino acids (aa) and is encoded by an open reading frame (ORF) of nucleotides 1112 to 2317 of (I). The aveR2 gene product has a protein sequence of 235 aa and is encoded by an ORF of nucleotides 2314 to 3021 of (I).

INDEPENDENT CLAIMS are also included for the following:

- (1) an isolated polynucleotide molecule (Ia) homologous to a polynucleotide molecule comprising nucleotides 1112 to 2317 of (I);
- (2) an isolated polynucleotide sequence (Ib) that naturally flanks the aveR1 open reading frame (ORF) of *S. avermitilis* in situ comprising nucleotides 1-1111 and 2318-5045 of (I);
- (3) an isolated polynucleotide molecule (Ic) homologous to a polynucleotide molecule comprising nucleotides 2314 to 3021 of (I);
- (4) an isolated polynucleotide sequence (Id) that naturally flanks the aveR2 open reading frame (ORF) of *S. avermitilis* in situ comprising nucleotides 1-2313 and 3022-5045 of (I);
- (5) an oligonucleotide molecule that hybridizes under highly stringent conditions to a polynucleotide comprising (I) or the complement of (I);
- (6) a recombinant vector (II) comprising (I);
- (7) a transformed host cell (III) comprising (II);
- (8) a substantially purified or isolated polypeptide (IV) comprising a sequence of 401 or 235 amino acids (as given in the specification), its homologous polypeptides or their fragments;
- (9) preparation (P1) of (IV);
- (10) a polynucleotide molecule (Ie) comprising (I) with at least one mutation that results in a detectable increase in the amount of avermectins produced by the cells of a strain of *S. avermitilis* compared to the cells of same strain that do not carry the gene mutation;
- (11) a genetic construct (GC) comprising (Ie) for introducing a mutation into either or both of the aveR genes;

(12) identifying a mutation in the aveR genes in a species or strain of S. avermitilis by comparing the amounts of avermectin produced by mutant and non-mutant strains and detecting the mutation from the increased amount of avermectins produced by the mutant strains;

(13) preparation (P2) of genetically modified cells of S. avermitilis;

(14) a strain of Streptomyces, producing increased amount of avermectins as a result of mutation in aveR genes; and

(15) an antibody (Ab) directed against aveR1 or aveR2 gene product.

ACTIVITY - Antiparasitic; insecticide.

MECHANISM OF ACTION - Avermectin polyketide synthase regulator. No supporting data given.

USE - (I) is useful for increased production of avermectins which comprises culturing the cells of species or strains of Streptomyces comprising mutated aveR genes (claimed). (Ie) is useful to mutate aveR genes (claimed). Avermectins are highly active anti parasitic agents having particular utility as anthelmintics, ectoparasiticides, insecticides and acaricides and useful for treating various diseases or conditions in humans, particularly those caused by parasitic infections.

ADVANTAGE - Avermectins prepared are effective against various nematodes, parasites including gastrointestinal parasites, ectoparasites, insects and other organisms, thus providing a wide range of treatment.

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